

Epidemiology of infection by serotypes D to K of *Chlamydia trachomatis**

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SUMMARY Non-specific urethritis (NSU) is a sexually transmitted disease; 50% of cases are due to *Chlamydia trachomatis*, so that this is the commonest sexually transmitted infection in the developed world. Chlamydial infection is now readily diagnosable and the evidence increasingly suggests that it is underdiagnosed. Chlamydial conjunctivitis (in the newborn baby or the adult) in the developed world is a complication of sexually transmitted genital infection by *C trachomatis* and it indicates a large reservoir of such infections. Because of the association of sexually transmitted diseases, systemic treatment for such chlamydial conjunctivitis should not be given until full genital and serological investigations have been carried out. Chlamydial infection causes serious complications (that were formerly often thought to be gonococcal), such as epididymitis in young men and salpingitis in young women. It may cause local complications in the eye of the newborn baby and even pneumonia in babies and fatal endocarditis in adults.

The diagnosis of NSU should lead to the correct treatment of the male patient and of his sexual partners. It is the promiscuous woman, who does not have a regular sexual partner to report back to her that he has NSU, who is at particular risk of undiagnosed chlamydial infection. Routine genital investigations for chlamydia are particularly indicated in her case.

Following the parallel of gonorrhoea, it seems that the use of contact tracers may be an effective method for controlling chlamydial infection.

Introduction

Urethritis is gonococcal or nongonococcal. Nongonococcal urethritis (NGU) is due to many specific causes identifiable by history and simple investigations; these include the sexually transmitted infestations and infections due to *Trichomonas vaginalis* and herpes genitalis as well as agents which are not sexually transmitted—for example, urinary tract infections causing secondary bacterial urethritis, chemicals, and trauma by instruments, catheters, and foreign bodies. Exclusion of these causes by history and simple investigations leaves what was called non-specific or abacterial urethritis (NSU), for which no specific cause could be ascribed. The development of efficient investigations for

chlamydia (particularly cell culture) has shown that about 50% of cases of NSU are due to the D to K serotypes of *Chlamydia trachomatis*.¹⁻⁶ In patients with frank discharge, the isolation rate may reach 75%.⁶

NON-SPECIFIC URETHRITIS

It will be many years before small clinics have the facilities for investigations for chlamydia. Until they do the diagnosis of NSU (always a sexually transmitted infection) is a useful pragmatic one that should lead to correct treatment and management of the patient and sexual contacts. Both chlamydial and non-chlamydial NSU respond to tetracycline.

NONGONOCOCCAL URETHRITIS

NGU was first reported in England and Wales in 1951 when there were 10 794 cases in men; by 1974, these had increased to 72 425 in men alone compared with 59 754 cases of gonorrhoea in men, women, and children. Allowing for the female partners of the men with NGU and for babies with chlamydial ophthalmia, total cases must have numbered over 140 000 in the year. Thus NGU is the commonest disease

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complex reported from clinics in England and Wales. Because over 90% of NGU is NSU (and about half of that is chlamydial) it seems that chlamydial infection is the commonest sexually transmitted infection in England and Wales, the United States,^{7,8} and probably in the developed world.

In 1951 at the Whitechapel Clinic, 751 cases of NGU were diagnosed; in 1976 (partly as a result of improvements in diagnosis) this number had increased to 2333 (an increase of 196%), of which 2161 (97%) cases were due to NSU.

OPHTHALMIA NEONATORUM

Infection of the conjunctiva in the developed world may be likened to the tip of an iceberg indicating a massive reservoir of genital infection. Thus, Neisser in 1897⁹ originally described *Neisseria gonorrhoeae* in material from the eyes of newborn babies and the genital tracts of adults. Soon ophthalmia neonatorum was recognised as gonococcal or nongonococcal, the latter being due to bacteria other than *N. gonorrhoeae* or abacterial. Over 90 years ago, Kroner in 1884¹⁰ thought that the nongonococcal forms were due to infection from the genital tract of the mother. After Halberstaedter and von Prowazek in 1907¹¹ described the inclusions now known by their names, these inclusions were found in conjunctival material from newborn babies and adults with conjunctivitis and in genital material from adults. After 50 years had elapsed, culture in yolk sac by T'ang and others in 1957¹² first permitted isolation of *C. trachomatis* from infected sites. Culture in cell culture¹³ is more effective than in yolk sac;¹⁴ it has been modified and made even simpler and more sensitive. Thus we can now readily isolate the agent from affected babies, from over 90% of their mothers,^{15,16} from the fathers with NSU, from about 50% of men attending clinics with NSU (as already noted), and from the eyes of young adults who present with chlamydial conjunctivitis and from their genital tracts.¹⁷

Chlamydial infection in pregnancy

Prospective studies of pregnant women in the United States of America have shown that about 5-13% may yield chlamydia-positive cervical secretions; about half of the babies born to culture-positive women develop clinical conjunctivitis but more are infected, as shown by the presence of antichlamydial antibody in tears or serum.¹⁸⁻²⁰ Chlamydial pneumonia may develop even without previous clinical conjunctivitis.²¹⁻²³ Schachter and others²⁴ reported an estimated incidence of chlamydial infection of 28/1000 live births with 14 cases of conjunctivitis and eight of pneumonia in a study in San Francisco.

Incidence of chlamydial and gonococcal ophthalmia
Chlamydial ophthalmia neonatorum (formerly called inclusion conjunctivitis or inclusion blenorhoea) is much commoner than gonococcal ophthalmia neonatorum.¹⁶ In the time that 34 babies with chlamydial ophthalmia were seen at the London Hospital and Institute of Ophthalmology, only five were seen because of gonococcal ophthalmia neonatorum; a previous study reported this ratio as 44 : 8.²⁵ Similarly, in the time that 153 adults were seen because of fresh chlamydial infection of the eye, only one adult with gonococcal infection of the eye was seen. The difference reflects the higher prevalence of chlamydial infection of the genitalia and the fact that chlamydial urethritis is often less productive of symptoms than gonococcal urethritis, so that it more often remains undetected. Thus investigation of the overnight urethral secretion may be necessary to make the diagnosis of NSU or chlamydial urethritis.^{26,27}

COMPLICATIONS OF CHLAMYDIAL INFECTION

Chlamydial ophthalmia neonatorum is more serious than formerly thought. It is a local manifestation of a more generalised infection in the baby.²⁸ It indicates potentially serious infection in the mother with certainty and in the father with strong probability. Pelvic inflammation is common in infected mothers after delivery.^{15,16,29,30} Isolation of *C. trachomatis* from infected Fallopian tubes has confirmed that this agent is a major cause of salpingitis;³¹⁻³³ isolation from Bartholin's ducts shows that it causes bartholinitis.³⁴ It is the commonest cause of epididymitis in young men.³⁵ Because *C. trachomatis* is sexually transmitted, it is commonly associated with other sexually transmitted infections;^{3,15,16,29,34,36,37} thus ophthalmia neonatorum may be due to gonococci and chlamydia together,¹⁶ just as may genital infection in adults.

Chlamydial ophthalmia neonatorum may cause local complications in the eye if treatment is started after the thirteenth day of life,³⁰ or if reinfection occurs.³⁸

The incubation of chlamydial ophthalmia is often longer than that of the gonococcal form, but chlamydial ophthalmia may be present at birth and both forms may occur after caesarian section, if this is carried out after the membranes have ruptured. Infants are commonly premature,¹⁶ which may be due to infection of fetal membranes over the infected cervix.

In one series of 25 mothers of infected babies,¹⁵ only 19 of the fathers were examined. As with gonococcal ophthalmia there is sexual instability in the parents of the affected babies; not all of the "fathers" were the natural fathers of the babies; they were the current sexual partners of the mothers.

TABLE 1 Development of chlamydial urethritis —Mr H, a student aged 24 years, was father of a baby with chlamydial ophthalmia neonatorum; his wife* was chlamydia-positive

Age of baby (weeks)	LMI (days)	Symptoms	Urethritis	Urethral PMNL/HPF	Hours urine held	Chlamydial culture result
5	5	None	No	3	7	—
12	21	None	No	2	5½	—
13	1	Urethral discharge (1 day)	Yes	10	2	+
14	8	Urethral discharge (8 days)	Yes	100	9	+

*Mrs H had a positive cervical culture result for chlamydia after one week's treatment with oxytetracycline 250 mg four times daily and a negative result after 500 mg four times daily for two weeks

+ Positive — negative

LMI = last marital intercourse

PMNL = polymorphonuclear leucocytes

HPF = high power field ($\times 1000$)

Table I shows the development of urethritis in one father (Mr H*) after resumption of marital intercourse when the baby was just over 4 weeks old. It seems that this man infected his wife before or during her pregnancy. His urethritis had cleared, to recur when his baby was just under 13 weeks old. *C. trachomatis* could only be isolated when he had urethritis. After one week of treatment with oxytetracycline 250 mg four times a day by mouth (after milkproduct-free meals), *C. trachomatis* was again isolated from his wife from cervical material. Since then a standard treatment of oxytetracycline 500 mg, four times a day for 14 days, has been used.

It is now becoming clear that *C. trachomatis* may cause serious complications, some of which resemble infection by *Chlamydia psittaci*. Thus, apart from infection of sexual partners and the eyes of newborn babies, spread of infection from genitalia to the eye, salpingitis, and epididymitis, *C. trachomatis* has been shown to cause endocarditis that was only diagnosed after the death of an adult with a previously normal heart,³⁹ and to cause pneumonia in babies.²¹⁻²³

EXPERIMENTAL CHLAMYDIAL URETHRITIS

Chlamydia-positive urethritis has been produced in male baboons by inoculation with cultures of D to K serotypes of *C. trachomatis* by different workers.⁴⁰⁻⁴¹ The latter authors produced urethritis that remained chlamydia-positive for three months; of four attempts at reinfection, three were successful; in each case urethritis remained isolate-positive for less than 15 days. Reinfection is obviously possible in subhuman primates (and man) but partial immunity may develop.

MANAGEMENT OF GENITAL INFECTIONS

Some recurrences of NSU are due to inadequate treatment and follow up. Others are due to defective

*The initials used in the case histories are those of a coding system.

management so that infected sexual partners are not treated. Thus, Mr NT, a medical worker aged 26, was seen because of chlamydia-positive urethritis, only nine days after he had been told he was "cured" of NSU after a five-day course of tetracycline 500 mg twice daily at another hospital. He denied having had sexual intercourse (or contact) since this treatment. This patient had had no less than four previous attacks of NSU in the two years before attendance. On only one of these occasions had his then regular girlfriend been treated; that was with a similar short course of tetracycline and was not concurrent with his treatment, so that "ping-pong" reinfection may have occurred. After treatment with doxycycline 200 mg daily for 14 days smears of the overnight urethral secretion on three occasions with cultures for chlamydia gave negative results.

The female sexual partners of men with chlamydial urethritis commonly have chlamydial infection of the cervix and the urethra.^{1-2, 42} Chlamydia may also be isolated from the rectum of such women⁴³ and, rarely, from the throat,^{44, 45} as well as from the urethra, the rectum, and the throat of male homosexuals.⁴⁶ Contact tracing for NSU usually results in the attendance of subsequent, rather than source, contacts, but Oriel and others⁴⁷ isolated chlamydia from eight of 13 source contacts and from six of 24 subsequent contacts.

HYPERENDEMIC TRACHOMA (SEROTYPES A-C)

In the developing countries hyperendemic trachoma due to serotypes A to C of *C. trachomatis*, which is the commonest eye disease in the world, may affect up to 90% of children in areas of high prevalence by the age of 1 year. The disease is spread by eye-to-eye transmission ("ocular promiscuity"), by flies and poor hygienic practices.⁴⁸ Spread is helped by the lack of piped water for washing and the persistence

of infectious discharges from the eye. Some 500 million people are affected and some two million are blinded.⁴⁹ The disease is caused by infection and superinfection by the A, B, Ba, and C serotypes of *C trachomatis*, together with superadded bacterial infections.

OCULAR INFECTION (SEROTYPES D-K)

In the developed countries, the D to K serotypes of *C trachomatis* infect the genital tract and cause chlamydial infection of the eye because of contamination with infected genital secretion. Such material was probably the cause of most cases of "swimming bath conjunctivitis." Only rarely will a sibling of an infected baby, or an adult, develop chlamydial infection of the eye because of contamination of the eye with infected ocular material.

In a series of 23 adult women who had presented because of isolate-positive ocular infection, *C trachomatis* was isolated from the genital tract in 19 cases; from the cervix in 19 of 21, the urethra in seven of 13, and the rectum in 10 of 22.¹⁷ One of these patients (Mrs OD; table II) had had chlamydial conjunctivitis for eight months and had probably harboured the organism for three years in genitalia and rectum, where she had the most marked mucosal changes.⁴³ Certainly genital infection may persist for prolonged periods. Schachter and others³ have reported persistence of chlamydial infection of the genitalia for one year in a man and for 11 months in a woman. Rees and others⁵⁰ reported persistence of chlamydial infection for up to 19 weeks in 18 women and for one year in another.

TABLE II Case histories of a married couple with chlamydial infections for over three years

MRS OD, a model, married for 4 months, seen on 14 April 1970.
History—sore left eye for 8 months, treated with Alucid and referred to Moorfields Eye Hospital; diagnosis, TRIC punctate kerato-conjunctivitis (TPK). Last marital intercourse occurred 1 day before; premarital intercourse for 3 years; husband only partner. Cervix showed "follicles" and pus cells (60/HPF); rectum showed giant "follicles" and pus cells (20/HPF).
Culture—eye, cervical, and rectal cultures chlamydia-positive.

MR OD, seen on 21 April 1970.
History—last marital intercourse 8 days before; premarital intercourse for 3 years; no other contact for more than 3 years.
Symptoms—occasional slight dysuria.
Signs—slight urethritis. *Microscopy*—first-voided urine: shreds (14 PMNL/HPF); second urine: clear; urine held for 14 hours.
Culture—Meatal swab and urethral scrape chlamydia-positive.

PMNL = polymorphonuclear leucocytes; HPF = high-power field

CONTACT TRACING

Of the male sexual partners of the 23 women reported by Vaughan-Jackson and others,¹⁷ 10 were examined. *C trachomatis* was isolated from urethral

TABLE III Case histories of three patients with chlamydial infections associated with gonorrhoea

MRS TI, aged 22, a computer operator and barmaid from Eastbourne.

History—November 1976: conjunctivitis diagnosed and treated with cephalexin tablets. 8 February 1977: chlamydia-positive conjunctivitis diagnosed and treated with doxycycline 300 mg immediately and 100 mg daily for 21 days; same treatment given to husband (Mr TI). 12 July 1977: chlamydia-positive conjunctivitis diagnosed and treated locally. 3 August 1977: genital investigations performed; chlamydia-positive cervicitis and urethritis diagnosed; cervical and urethral cultures positive for *N gonorrhoeae*.

MR TI, aged 23, a lift repairer from Eastbourne.

History—February 1977: treated with doxycycline 100 mg daily for 21 days.

Symptoms—none; on examination, urethritis after holding urine for 12 hours.

Microscopy—Gram stains showed 200 PMNL/HPF.

Culture—negative culture result for *N gonorrhoeae*, positive result for *C trachomatis*.

MR JT, aged 25, an asphalter from Eastbourne.

Symptoms—urethral discharge for 6 weeks, bilateral testicular pain for 1 week. On examination, bilateral epididymitis.

Culture—positive results for *N gonorrhoeae* and for *C trachomatis* (developed postgonococcal urethritis).

MRS IH, divorced, aged 22, housewife from Eastbourne.

Symptoms—abdominal pain for two weeks. Appendectomy performed, bilateral salpingitis found; treated with ampicillin and penicillin intramuscularly for 7 days.

Culture—negative results for *N gonorrhoeae* and *C trachomatis*.

Serology—LGVCFT positive (1/64); micro-IF test positive; ≥256 A-K.

material from five (including Mr OD; table II), all of whom had urethritis.

Control of a sexually transmitted disease must include control of infection in the sexual partners.

The case of Mrs TI (table III), in which conjunctivitis recurred until suitable contact tracing had been carried out, illustrates this point and the association of chlamydial infection with other sexually transmitted infections. Examination showed chlamydial infection of the genitalia which had recurred despite her having been given doxycycline for herself and her husband (Mr TI) (without previous genital examination). It also showed that she had gonorrhoea, which was found in her extramarital consort (Mr JT), who had been virtually symptomfree until he had developed epididymitis. Chlamydial urethritis was present in her husband. Her extramarital consort had both chlamydial and gonococcal urethritis with epididymitis. One of his contacts (Mrs IH) had developed acute abdominal pain, diagnosed as due to appendicitis. Operation showed that she had acute bilateral salpingitis that was virtually certainly chlamydial with or without gonococcal infection.

Male contacts of women with chlamydial conjunctivitis included Mr VZ, aged 21, the regular sexual partner for three years of a woman with chlamydial

conjunctivitis and genital infection. He had had a slight urethral discharge for two months, which was found to be chlamydial. Five months earlier he had been successfully treated for NSU elsewhere; but neither his regular sexual partner nor his other recent contact had been seen so that "ping-pong" reinfection resulted and his regular sexual partner developed chlamydial infection of the eye.

Of 21 men with chlamydial infection of the eye,¹⁷ chlamydial urethritis was present in eight. An additional four who had no evidence of urethritis and had negative genital culture results for chlamydia had female sexual partners who harboured chlamydia in the genital tract; this suggests that immunity of the genital tract may develop and may not parallel that of the eye.

The incidence of chlamydial infection of the genitalia in women attending clinics in the United Kingdom varies from 12% to 31%.^{37 47 51-54} It seems no coincidence that the highest incidence was found in a clinic⁵⁴ in which the contacts of men with NSU were not routinely seen and treated.

The use of contact tracers at the Whitechapel Clinic of The London Hospital led to a 20% decrease in the incidence of gonorrhoea at a time when the national incidence had increased by 33%. The decrease was in the number of infected men attending because the number of infected women attending had increased. Thus the ratio of infected women to men was 1:3.9 in 1960 and 1:2.2 in 1969.⁵⁵

Following the parallel of gonorrhoea, it is likely that the use of contact tracers may provide an effective way of improving the control of chlamydial infection.

Conclusions

NSU is a sexually transmitted disease and about 50% of cases are due to *C. trachomatis*. A diagnosis of NSU in men does not require complicated investigations and should lead to the examination of the sexual partner(s), the exclusion of other sexually transmitted diseases, and effective treatment with tetracycline, which is effective against chlamydial and non-chlamydial NSU.

The promiscuous woman, who does not have a regular sexual partner to report to her that he has urethritis, is at special risk of having undetected chlamydial infection of the genitalia. Routine genital investigations for chlamydia are particularly indicated in her case.

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